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Running title: enhancing decision-making re adjuvant chemotherapy in breast cancer

Enhancing decision-making about adjuvant chemotherapy in early breast cancer following EndoPredict testing

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Objective: Chemotherapy side-effects can be substantial. There is increasing recognition that some oestrogen receptor positive (ER+ve), human epidermal growth factor receptor 2 negative (HER2–ve) patients with breast cancer derive no benefit from chemotherapy and experience only iatrogenic harm. Gene expression profiling tests help refine recurrence risk and likely chemotherapy benefit. EndoPredict® is one such test, which classifies risks of distant recurrence as low or high in patients treated with surgery and adjuvant endocrine therapy alone. We compared treatment decisions pre and post test results, patients' anxiety, decisional conflict and oncologists' confidence about the decisions made.

Methods: 14 oncologists in 7 UK hospitals saw 149 pts judged to have equivocal indications for chemotherapy. Provisional treatment decisions were recorded then reconsidered when EPclin results were available. Pre and post test results, patients completed State/Trait Anxiety Inventories (STAI) and the decisional conflict scale (DCS). Oncologists also recorded basic clinical details, their agreement with, and confidence about treatment decisions.

Results: 67% patients initially prescribed endocrine alone with high risk result upgraded to endocrine+chemotherapy (E+C); 83% prescribed E+C and had low risk scores, downgraded to E. None of 46 patients initially favouring E alone, who were low risk changed decisions. Oncologists' confidence about decisions was significantly increased following the results ($p=0.002$). Patients with downgraded treatment decisions had significantly lower anxiety scores ($p=0.045$); those upgraded had increased scores ($p=0.001$). Overall decisional conflict and uncertainty fell significantly post-test ($p<0.022$).

Conclusions: EndoPredict scores increased oncologists' and patients' decision-making confidence, generally improving the matching of risk with therapy decisions.

Keywords: Gene expression profiling, EndoPredict®, decision-making, anxiety, breast cancer, communication, cancer, oncology, treatments, oncologists

Background

Balancing the harms as well as the putative benefits of all breast cancer treatments is a vital component of decision-making. Side-effects of chemotherapy such as hair loss, fatigue, nausea and vomiting can be substantial and exert a deleterious impact on body image and quality of life¹. Coping with some of these side-effects may be more tolerable if patients feel that the risks of recurrence are significantly reduced. Conversely over-treatment with drugs that make little or no difference to a patient's recurrence risk needs to be avoided. Establishing the risk of early and late stage recurrence in early breast cancer can be capricious. Historically features including tumour size, histological grade, type, nodal involvement and lympho-vascular invasion were seen as useful prognostic indicators; these characteristics, together with biomarkers such as oestrogen receptor/progesterone receptor (ER/PR) and human epidermal growth factor receptor (HER) status, help to determine which patients have a greater risk and therefore potentially better outcome with and without adjuvant therapy². As further data emerge regarding the longer term risks of distant recurrence, certain tests may also help to determine how long patients should be encouraged to continue with endocrine therapy.

More recent biomarker research has focused on the development of prognostic and ultimately predictive tests to ensure that systemic endocrine and/or chemotherapy is only given to those patients with tumour characteristics that might make response more likely and worthwhile. The gene expression profiling tests such as Breast Cancer Index, MammaPrint® and OncotypeDX® can assist in the estimation of risk of recurrence³. EndoPredict® is another multigene expression profiling test for predicting the likelihood of distant recurrence in patients with ER-positive, HER2-negative breast cancer treated with adjuvant endocrine therapy only⁴. The test reports an EP score, using just the molecular parameter and an EPClin score that includes relevant clinical parameters. Two large randomized phase III trials [Austrian Breast and Colorectal Cancer Study Group (ABCSG)-6 and ABCSG-8] have shown that the test can identify subgroups that have differences in their 10-year distant recurrence rates⁵. Additionally, the EP/EPClin classifier adds substantially prognostic information to clinico-pathological parameters, including Ki67 staining⁴. A retrospective review on tissue blocks from the ATAC study also showed that integrating tumour size and nodal status with the molecular data, increased prognostic information⁶. The EPClin score can help clinicians by delineating the risks

of distant recurrence as low or high for ER+, HER2-negative patients treated with adjuvant endocrine therapy alone.

Because of the many advances made in diagnostic testing, surgical and radiotherapy techniques and the many new systemic therapies available, decision making about treatment options in breast cancer has become more complex. Patients may need to make multiple decisions within a short space of time and all conversations take place against a backdrop of fear and uncertainty. Health literacy and numeracy are often quite poor and lay populations generally subscribe to the notion that in the context of life-threat, more treatment must be better than less. Given the fears about the potential for death from metastatic breast cancer, it is not surprising that both patients and clinicians will consider every additional therapeutic option with a resultant potential overtreatment with systemic chemotherapy⁷.

For some patients with early stage breast cancer, the clinic-pathologic features of the tumour such as size, nodal, ER and HER2 status are sufficiently clear for oncologists to either recommend or omit adjuvant chemotherapy. Some have found visual aids such as PREDICT or Adjuvant!, which show survival benefits with or without adjuvant hormone and chemotherapy helpful, although understanding of the graphs from these is dependent on basic numeracy. There is research demonstrating that genomic test scores may permit clinicians to discuss the pros and cons of chemotherapy treatment recommendations with more confidence and may help patients to make more informed choices⁸. Provision of the risk of recurrence from a gene expression profiling test such as EndoPredict may help in those situations where the likely benefit of adjuvant chemotherapy is equivocal. Only one small Austrian study previously has shown that Endopredict results can alter the decision to recommend chemotherapy made using traditional clinical parameters⁹.

In this study we compared pre and post EndoPredict test results: - adjuvant treatment decisions, the patients' anxiety, their decisional conflict and oncologists' confidence about decisions made.

Methods

A non-randomised prospective cohort study measuring decision-making for adjuvant chemotherapy before and after EndoPredict testing. Study objectives included:-

- 1) comparison of treatment decisions before and after EndoPredict test results

- 2) measurement of the cost-utility of EndoPredict testing (to be reported separately)

The primary psychosocial outcomes were the impact that knowledge about the risk of recurrence had on anxiety and decisional conflict of patients, and oncologists' confidence about the treatment decisions made pre and post-test.

The primary quantitative outcome was the change in decision made by the patient and clinician about adjuvant chemotherapy as a result of the additional information in the EndoPredict test.

Participants were recruited to the study between July 2015 and October 2016 from 7 UK hospitals by 14 breast cancer specialist oncologists. Written informed consent was obtained prior to all data collection. Ethical approval (South Central – Oxford C Research Ethics Committee ref: 15/SC/0090), and NHS R&D permissions were obtained for each centre and adopted by the NIHR Portfolio (ref: 19287). Women with early stage, ER+ HER2-negative breast cancer who were judged by their multidisciplinary teams (MDTs) to have equivocal indications for chemotherapy and able to read English, were eligible to join the study.

Recruitment

Post-operatively prospective patients were discussed by their treating multi-disciplinary team (MDT). Those identified as potentially eligible were either given a Patient Information Sheet (PIS) by a member of the breast team at the post-surgical review, or sent a covering letter and PIS in the post prior to their first oncology consultation.

The treating oncologist discussed histological results including size, grade, nodal status, ER and HER-2 status with patients as part of their normal care, and used standard clinical-pathological criteria to estimate the likely benefit from adjuvant chemotherapy. Those patients judged by the MDT to be in an intermediate risk group using standard clinico-pathologic criteria were asked by the oncologists, after a careful consideration of the facts, to make a provisional treatment decision – either to have or to omit adjuvant chemotherapy. These shared decisions were recorded together with the chemotherapy regimen if appropriate in the notes and on the CRF (see appendices 1a & b).

Eligible patients who had read the PIS had a discussion about the EndoPredict test with their oncologist. If they consented to the study, their tissue was sent for analysis

and an appointment made for a further consultation. A provisional referral for chemotherapy was made to minimise any delay in subsequent treatment whilst awaiting the test result.

Patients and oncologists met for a second consultation within 2 weeks when the EndoPredict test results were available and the decision about adjuvant chemotherapy reviewed. Patients completed the Decisional Conflict Scale (DCS)¹⁰ and the Spielberger (STAI) trait and/state anxiety questionnaire¹¹ following their initial decision-making and the DCS and STAI (state) after the risk of recurrence scores had been discussed. Oncologists recorded their confidence in the decision made at both time points.

Assessments

The DCS assesses an individual's uncertainty when choosing between options, and factors contributing to that including feeling uninformed and unsupported. Decisional conflict can also be affected by issues such as pressure from others, lack of clarity about options, pre-existing or unrealistic expectations. All of these are areas that might be experienced by women considering adjuvant therapy. The DCS is comprised of 16-items with a 5-point Likert categorical response scale: 'strongly agree', 'agree', 'neither agree nor disagree', 'disagree' and 'strongly disagree'. It provides a total score from all 16 items and 5 possible sub-scores (informed, values clarity, support, uncertainty and effective decision). Total scores range from 1-100 with higher scores denoting more decisional conflict. The instrument has good psychometric properties.

The STAI consists of 2 questionnaires with 20 items rated on simple 4 point scales. It is one of the most widely used well-known, validated research clinical tools for evaluating anxiety proneness (Trait) and the current state of anxiety or anxiety change (State). It is self-administered and takes approximately 10 minutes to complete and it has been used successfully in many breast cancer studies. High STAI scores signify greater anxiety. The Trait anxiety is measured only once and the State at each time point.

Oncologists completed forms about provisional treatment decisions and confidence in their decisions based on the usual clinic-pathologic features and again following their consultations with patients when EPclin scores were available (Appendices 1a &b).

Statistical Methods

Standard scoring rules were followed for the DCS and STAI. Means and change scores were calculated and paired t-tests or Chi2 statistics used as appropriate to determine significance of these between initial and post EndoPredict test decisions.

Doctors' confidence pre and post-test was compared using Chi2 statistics.

Pre and post-test means and score changes for the STAI and DCS scales were compared using T-tests.

All scores were based on raw data, without imputation. DCS responses were originally based on a 1-5 scale where 1=strongly agree and 5=strongly disagree, and converted to percentages. DCS sub-scales were calculated where there were 2 or more responses. Total DCS scores were calculated where there were 2 or more responses for all sub-scales. STAI scores were calculated where there were fewer than 2/20 missing responses.

Results

One hundred and fifty-one patients were enrolled into the study of whom 149 were eligible and completed the study. (2 patients did not have EndoPredict test data available for evaluation for technical reasons). Table 1 shows patient characteristics.

Insert Table 1

The median Nottingham Prognostic Index was 3.76. Of 149 tested tumours, 99 had no evidence of nodal metastases, 29 had macro-metastases and a further 21 micrometastases alone. All patients were ER positive and Her-2 negative as entry criteria for the trial.

EndoPredict test results

The initial **shared** decision for 88 patients (59.1%) was endocrine treatment alone and for 61(40.9%) endocrine therapy plus chemotherapy. Table 2 shows that of those favouring endocrine treatment alone initially 42 had high risk EPclin scores and 66.7% of these upgraded to endocrine and chemotherapy. None of the 46 patients who initially favoured endocrine alone and who had low risk EPclin scores had a change in decision. The 32 patients who had initially opted for endocrine and chemotherapy with high risk EPclin scores generally kept to that decision although 3 (9.4%) downgraded to endocrine alone. The patients with low risk scores mainly downgraded to endocrine alone although 5 (17.2) kept to their original decision.

Insert Table 2

In response to the statement “*as the treating clinician I am confident with the decision made today*” oncologists were significantly more likely to strongly agree post-test (50%) compared to pre-test (8%) $P=0.002$.

Patients’ Anxiety

STAI state anxiety scores were stable in patients with unchanged decisions for endocrine alone or endocrine plus chemotherapy. Those patients whose therapy was downgraded (27/61) had significantly lower state anxiety scores ($P=0.045$) whereas those whose treatment was upgraded had increased scores ($P=0.001$). There was no significant difference in state scores pre-post test in those who had high or low trait anxiety.

Decisional Conflict

Table 3 shows the total scores and the 5 subscale scores on the DCS. Post-test patients were less uncertain, more informed and felt more effective. Decisional conflict was reduced significantly ($P=0.022$) but this was influenced by those patients whose treatment remained unchanged (94/149).

Insert Table 3

Table 4 shows that patients with unchanged decisions had significantly lower uncertainty scores (mean change 4.78, $P=0.001$). In those for whom treatment was downgraded, it fell slightly ((27/149) mean change 1.87) and uncertainty increased (mean change -1.07) where treatment was upgraded (28/149).

Insert Table 4

Discussion

The appropriate use of gene-expression profiling tests has the potential for maximising benefit and reducing iatrogenic harm. This study showed that EPCLin test results increased oncologists’ and patients’ decision-making confidence. The matching of risk scores with therapy decisions was mainly improved although some post-test decisions need further examination. Our results are similar to other prospective decision impact studies using 21 gene assays where adjuvant treatment decisions changed in at least 25% of patients and decisional conflict decreased too^{9, 12-13}.

All decision-making requires the balancing of likely absolute benefits in terms of preventing recurrence versus the treatment related side effects. Health literacy and numeracy skills in the general population are often poor thus explaining risk and uncertainty can be confusing especially when set against a backdrop of fear and

anxiety. We do not know from this study why some patients with a high risk score did not wish to have chemotherapy or why those with low scores chose to have chemotherapy nevertheless. One can hypothesise that fear or anecdotal experience of others known to the patients might have had an influence. Another possible explanation is that the oncologists themselves had other idiosyncratic reasons for endorsing and altering suggestions about treatments. Healthcare professionals' own communication about risks harms and benefits are subject to unconscious bias and misunderstanding. Interesting research has identified that all individuals (this would include health care professionals as well as patients) have different tolerances to uncertainty. Those with a high intolerance to uncertainty might have inadvertently communicated scores in a somewhat nuanced, negative manner especially if the score were borderline low or high risk.

Clinical implications

There is recognition that not all women with early breast cancer need or benefit from adjuvant chemotherapy. Many lay populations feel that in the context of life threatening disease more treatment must be better. Gene expression profiling tests provide a risk of recurrence score that should enable wiser decision-making. This study showed that in general the receipt of risk scores helped doctors feel more confident about decisions. Patients felt less decisional conflict and for those who had treatment decisions downgraded from chemotherapy to no chemotherapy, anxiety significantly decreased.

Study limitations

This was a small study and had a few surprising findings as not all decisions appeared rational. Further work needs to be done exploring the communication of risks of recurrence scores with anxious patients. It would be interesting to ascertain why some patients persisted with chemotherapy despite having low risk scores. Finally more information regarding the socio-educational background and understanding of recurrence might be helpful in future research.

Conclusion

As discussions about the logic and rationale behind different treatment recommendations for breast cancer have become increasingly complex, clinicians need an increased repertoire of communication skills to explain risks and benefits easily, or patients are probably not making informed choices about options.

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Conflicts of interest: The authors have no conflicts of interest to declare

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Table 1. Endopredict patient characteristics

Age (years)	
Mean (sd)	56.44 (10.90)
Range	26-77
Histology	
Ductal	115
Lobular	28
Multifocal	6
Tumour Grade	
I	17
II	86
III	43
More than 1 tumour with different grades α	3
Nodal Metastases	None: 99 Macro: 29 Micro alone: 21
NPI*	Mean: 4.04, Mode: 3.24, Min: 2.16, Max: 14.40,
	Percentiles: 25:3.32, 50:3.76, 75:4.39
Invasive Tumour Size[√]	Mean: 25.15, Mode: 14.00, Min: 7.00, Max: 100.80
	Percentiles: 25:14.00, 50: 21.00, 75:28.00

Evaluable data was available for 149 patients, 2 consenting patients are not included in the data analyses because Endopredict test data was not available due to technical reasons. All patients were ER + and Her2 -.

α multifocal tumours, 1 patient had a medullary tumour of grade I and III, 1 patient had a mix of lobular tumour grade III and ductal tumour grade II and 1 patient had a ductal tumour of grade I and II.

* for 1 patient with multifocal tumour and two NPI scores, the lobular score was used

[√] 149 patients – calculations exclude invasive tumour sizes for additional smaller tumours for 10 patients

Table 2: Initial and final treatment decisions following EndoPredict test results

Initial decision		Test Result			Final Decision		
	N=149		N	%		N	%
endocrine	88 (59.1%)	High	42/88	47.7	Unchanged	14/42	33.3
					Upgraded to endocrine and chemotherapy	28/42	66.7
		Low	46/88	52.3	Unchanged	46/46	100
					Upgraded to endocrine and chemotherapy	0/46	0.0
endocrine and chemotherapy	61 (40.9%)	High	32/61	52.5	Unchanged	29/32	90.6
					Downgraded to endocrine alone	3/32	9.4
		Low	29/61	47.5	Unchanged	5/29	17.2
					Downgraded to endocrine alone	24/29	82.8

Table 3: Pre and post-test decisional conflict scores and sub-scores

	N	Pre-test Mean (SD)	Post-test Mean (SD)	Mean change	P-value
Uncertainty	144	27.49 (27.40)	21.76 (23.18)	5.73	0.025
Uninformed	144	16.15 (13.30)	12.67 (13.76)	3.47	0.009
Unclear	136	16.12 (14.71)	14.22 (15.59)	1.90	0.222
Unsupported	136	12.07 (12.58)	10.85 (13.85)	1.23	0.308
Ineffective	136	17.69 (14.68)	13.01 (15.20)	4.69	0.002
Total Conflict	136	17.74 (13.59)	14.59 (14.26)	3.15	0.022

Table 4: Comparison of pre- and post-test Decisional Conflict Scale scores by treatment decisions

Treatment decision	N	Missing	Pre-test Mean (SD)	Post-test Mean (SD)	Mean Change	P value
Upgrade from E to E+C	26	2	18.46 (13.99)	19.53 (15.50)	-1.07	0.668
Downgrade from E+C to E	24	3	19.99 (16.15)	18.12 (18.69)	1.87	0.726
Unchanged	86	8	16.90 (12.77)	12.11 (11.85)	4.78	0.001